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10/589,875	08/18/2006	Dirk Casimir Maria Leysen	074358-0104	3772

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
JAISLE, CECILIA M	
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1624	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,875	LEYSEN ET AL.	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-49* is/are pending in the application.

4a) Of the above claim(s) *34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,33 and 37-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08-18-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Abstract

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. As an aid to future researchers, a structural formula of the claimed compounds should be given

Complete revision of the content of the abstract is required on a separate sheet.

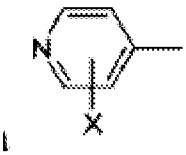
Lack of Unity

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions that are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

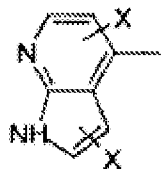
I. Claims 32, 33 and 37-49, drawn to compounds of Formula I, wherein Ring(1) is



I

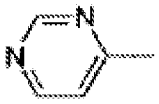
, classified in class 546, subclasses 265, 275.1, and 276.4, *inter alia*, and in class 544, subclass 333, *inter alia*, pharmaceutical compositions thereof and therapeutic methods using these compounds, classified in class 514, subclasses 318 and 326, inter alia.

II. Claims 32-49, drawn to compounds of Formula I, wherein Ring(1) is



, classified in class 546, subclasses 113, *inter alia*, and in class 544, subclass 333, inter alia, pharmaceutical compositions thereof and therapeutic methods using these compounds, classified in class 514, subclasses 256 and 300, inter alia.

III. Claims 32 and 37-49, drawn to compounds of Formula I, wherein Ring(1) is



, classified in class 544, subclass 328, *inter alia*, pharmaceutical compositions thereof and therapeutic methods using these compounds, classified in class 514, subclass 256.

IV. Claims 39-44 and 46-49, drawn to therapeutic methods using compounds of Formula I, wherein Ring(1) is other than as provided for by Groups I-III, variously classified in class 514.

Each group as set forth above lacks unity with each other group, i.e., there is no single general inventive concept. The unique special technical features in each group are the identities of the pyridyl ring of Formula I, Group I, Ring(1), of the pyrrolidino-pyridyl ring of Formula I, Group II, Ring(1), of the pyrimidinyl ring Formula I, Group III, Ring(1) and of compounds of Formula I, where Ring(1) is other than as provided for by Groups I-III. The technical relationship among the inventions does not involve at least one common or corresponding special technical feature. The expression "special

technical feature" is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. In this case, a reference that could be used to reject the methods of Group I could not be used to reject the methods of Group II-IV.

The Group I invention has special technical features not common to Groups II-IV and would be expected to be useful other than as disclosed, e.g., as hypertensive agents (US 4997834). The Group II invention has special technical features not common to Groups I, III and IV and would be expected to be useful other than as disclosed, e.g., as intermediates to compounds in the control or prevention of illnesses such as cancer (US 20080039460). The Group III invention has special technical features not common to Groups I, II and IV and would be expected to be useful other than as disclosed, e.g., as useful in the treatment of movement disorders such as Parkinson's disease (US 20080058356).

During a telephone conversation with Dr. Steven Reid on Mar. 20, 2008 a provisional election was made with traverse to prosecute the invention of Group I, claims 32, 33 and 37-49. To the extent that claims 32, 33 and 37-49 are directed to the elected subject matter, as defined above, they are under examination on their merits. Otherwise, claims 32, 33 and 37-49 are withdrawn from examination to the extent that they are not directed to the subject matter of Group I. Applicant must affirm this election in replying to this Office action. Claims 34-36 are withdrawn from examination as directed to non-elected subject matter.

To preserve a right to petition, the reply to this Office Action must distinctly and specifically point out supposed errors in the restriction requirement, or the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* inhibition of the PKC isoforms PKC epsilon, PKC gamma, PKC theta and PKC zeta, (pages 76-87, *inter alia*), does not

reasonably provide enablement for treatment or prevention of a metabolic disease or disorder in a mammal (claims 39, 45), where the disease or disorder is hyperglycemia, hyperinsulinemia, hyperlipidemia, insulin-resistant diabetes, lipoatrophies or obesity (claim 40, 41), where the disease or disorder is Type I or Type II diabetes, severe insulin resistance, Mendenhall's Syndrome, Werner Syndrome (WS), leprechaunism (Donohue syndrome), lipoatrophic diabetes, hypertension, osteoporosis or lipodystrophy (claims 42-44), inhibition of the activity of any kinase (claim 46-49). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

(1) Breadth of claims.

(a) Scope of the compounds. The claims cover method of using potentially billions of pyridine compounds of Formula (I).

(b) Scope of the diseases covered. The claims embrace treatment or prevention of a metabolic disease or disorder in a mammal (claims 39, 45), where the disease or disorder is hyperglycemia, hyperinsulinemia, hyperlipidemia, insulin-resistant diabetes, lipoatrophies or obesity (claim 40, 41), where the disease or disorder is Type I or Type II diabetes, severe insulin resistance, Mendenhall's Syndrome, Werner Syndrome, leprechaunism, lipoatrophic diabetes, hypertension, osteoporosis or lipodystrophy (claims 42-44), and inhibition of the activity of any kinase (claim 46-49). Therefore, the claims are of unknown scope.

Current medical knowledge emphasizes that many of the specifically named diseases/conditions require lifestyle changes, especially diet and exercise, for successful treatment. The major goal in treating Type II diabetes is to minimize blood sugar elevation without causing abnormally low blood sugar levels. Type II diabetes is treated first with weight reduction, diabetic diet, and exercise. When these measures fail to control the elevated blood sugars, oral medications are used. If oral medications are still insufficient, treatment with insulin is considered.

Chronic hyperglycemia that persists even in fasting states is most commonly caused by diabetes mellitus, and chronic hyperglycemia is the defining characteristic of the disease. Certain eating disorders produce acute non-diabetic hyperglycemia, e.g., the binge phase of bulimia nervosa, when the subject consumes a large amount of calories at once, frequently from foods high

in simple and complex carbohydrates. Certain medications increase the risk of hyperglycemia. A high proportion of patients suffering acute stress, e.g., stroke or myocardial infarction, may develop hyperglycemia, even absent a diabetes diagnosis. Hyperglycemia occurs naturally during infection and inflammation.

Treatment of hyperglycemia requires eliminating the underlying cause, *e.g.,* treatment of diabetes when diabetes is the cause. Acute and severe hyperglycemia can be treated by direct administration of insulin in most cases.

Treatment of hyperlipidemia itself includes dietary changes, weight reduction and exercise. If lifestyle modifications cannot bring about optimal lipid levels, then medications may be necessary.

Werner syndrome (progeria of the adult) is the most common of premature aging disorders. Werner syndrome is inherited as an autosomal recessive disorder of chromosome 8, meaning that a defective gene is inherited from each parent. The syndrome is estimated to occur in 1 in 1 million individuals. It affects both males and females. Werner syndrome has no cure or specific treatment.

Donohue syndrome (also known as Leprechaunism) is an extremely rare genetic disorder. Leprechaunism derives its name from the fact that those afflicted with the disease often have elfin features and are smaller than usual. Sufferers may also be insulin resistant. Early death is usual.

Impaired Glucose Tolerance (IGT) is a pre-diabetic state dysglycemia associated with insulin resistance and increased risk of cardiovascular pathology.

Although some drugs can delay the onset of diabetes, lifestyle modifications play a greater role in the prevention of the disease. Patients identified as having an IGT should exercise regularly and have a balanced diet removing sugar.

(2) The nature of the invention and predictability in the art: The nature of the invention is therapeutic use of the inventive compounds to treat all these diseases/conditions. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: Direction and guidance provided is very limited. The dosage range information is so meager, that it would require extensive experimentation to determine a specific dosage for a specific disease/condition, mode of administration and therapeutic regimen. Moreover, the dosage is generic; the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for the various types of diseases/conditions claimed.

(4) State of the Prior Art: Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions and other diseases recited for the inventive compounds. Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present,

> "The first paragraph of 35 U.S.C. 112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."

Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 65 USPQ2d 1452, 1456 (Fed.Cir. 2003).

Regarding the potential for PKC inhibitors in the treatment of diabetes, Cahoon, et al., http://www.mendosa.com/pkc.htm, downloaded 5/1/2008, reports:

> Roger Corder, professor of experimental therapeutics at the William Harvey Research Institute and the Barts and London School of Medicine, wrote a commentary in the September 2002 issue of *Clinical Science* discussing the potential future role of PKC-beta inhibitors in the treatment of diabetes-related complications.
>
> Corder states that based on animal studies—primarily with rats—LY333531 inhibits PKC-beta formation. In rat studies, this compound has normalized retinal and kidney vascular function, though not completely to the level of kidney function found in nondiabetic rats.
>
> More recent studies also show improvement of impaired nerve function in diabetic rats. Corder therefore speculates that PKC-beta inhibitors **will** play a role in the treatment of diabetes-related microvascular complications such as eye disease, kidney disease and nerve damage.
>
> He notes that phase 2 and 3 clinical trials, involving humans, are currently being conducted and adds that this novel drug **may** also have a role in treating macrovascular disease involving the heart and large blood vessels, although this remains to be proven in studies.
>
> Despite the potential held out by this new research, **the greatest weapon people with diabetes have is tight control of blood glucose. Near-normalization of blood-glucose levels remains the primary goal of diabetes treatment and care.**

Ring, et al., Diabetes, Vol. 52, March 2003, pp. 588-595, observed, "Our observation that GSK-3 inhibitor administration *in vivo* reduces fasting hyperglycemia in ZDF rats **suggests** an ability of these compounds to modulate net

hepatic glucose output." But, they stopped short of recommending a GSK-3 inhibitor for treatment of hyperglycemia.

Ciaraldi, et al., J. Diabetes and its Complications, 16 (2002), 69-71, point to a potentially promising future for GSK-3, "Given its effects on GS, GSK3 can also be expected to play a critical role in the pathogenesis of insulin resistance. Interventions that improve GS activity, possibly through GSK3, represent an area of potential therapeutic benefit."

Moller, Nature, Vol. 414, Dec. 13, 2001, 821-827, guardedly reports:

> GSK-3 has a clear role in opposing the effect of insulin, by inhibiting the activation of glycogen synthase and the subsequent accumulation of glycogen in muscle. Recent results with potent and selective inhibitors **suggest** that reducing GSK-3 activity *in vivo* could indeed augment insulin action, and that this **may** occur in multiple steps.

Ciaraldi, et al., Am. J. Physiol. Endocrinol. Metab., 291: 891-898, 2006:

> The major finding of the present work is that there is tissue specificity in the regulation of GSK-3 expression inhuman tissues in response to *in vivo* interventions that may provide insight into the roles of GSK-3 in different tissues. Changes in GSK-3 in skeletal muscle occur in the opposite direction from those in insulin action on whole body glucose disposal; insulin action goes up as GSK-3 goes down. These changes are independent of changes in BMI. Conversely, alterations in GSK-3 in adipocytes have more in common with changes in BMI. These responses **suggest** that therapeutic interventions targeting GSK-3 **could** result in improvements in both skeletal muscle insulin action and reducing adiposity.

Regarding possible connection between WS and a p38alpha MAPK inhibitor, Bagley, et al., Bioorg. Med. Chem. Lett. 17 (2007) 5107-5110, recommends further research:

> [The] inhibitor activity [of the p38α MAPK inhibitor VX-745] in HAC2 and WS [Werner Syndrome] cells was confirmed by ELISA and immunoblot assay, showing excellent selectivity for p38α MAPK over JNK. Given this selectivity profile, VX-745 **would appear** to be ideal for **further studies** of the accelerated ageing of WS cells in culture, which are now underway.

At present no known drug can successfully prevent or reverse the course of all conditions/diseases recited and encompassed by the present claims, despite the fact that many drugs are said to inhibit kinases involved in metabolic disease, such as PKC, JNK1, p38 kinase, GSK-3, IKKbeta (IKappaB kinase beta) and p70S6K activity (specification, page 33, *inter alia*). Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Thus, the state of the prior art recognizes that the inhibition of PKC, JNK1, p38 kinase, GSK-3, IKKbeta (IKappaB kinase beta) and p70S6K activity as an effective treatment of the specific diseases and conditions recited is an area for future research, especially as applied to human therapy.

(5) Working Examples: The specification provides enablement for *in vitro* inhibition of the PKC isoforms, PKC epsilon, PKC gamma, PKC theta and PKC zeta, (pages 76-87, *inter alia*), and claims directed thereto would be deemed allowable.

Although the specification refers to testing procedures, it is apparent that the only testing actually performed is with mice, because that is the only specific data reported. In addition, the specification tests offer no evidence establishing any connection between *in vitro* inhibition of the PKC isoforms PKC epsilon, PKC

gamma, PKC theta and PKC zeta, and any specific disease or condition recited in the claims, especially as applied to human patients. The *in vitro* inhibition of the PKC isoforms PKC epsilon, PKC gamma, PKC theta and PKC zeta, provides no correlation between any specific compound of the present invention and inhibition of any specific disease or condition. There is no indication that the testing reported in the present specification is art-recognized.

(6) Skill of those in the art: The prior art recognizes that no compound has ever been capable of treating all diseases or conditions recited by the present claims generally.

Discussions above of the skill of those in the art support that successful treatment of diseases caused by and/or associated with *in vitro* inhibition of the PKC isoforms PKC epsilon, PKC gamma, PKC theta and PKC zeta, is a subject for further investigation, especially as applied to human patients.

(7) The quantity of experimentation needed: Based on the content of the disclosure, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for the reasons stated above.

The consideration of the above factors demonstrates that the present application sufficiently lacks enablement of the present claims. In view of the breath of the claims, the pharmaceutical nature of the invention, the unpredictability of relationship between *in vitro* inhibition of the PKC isoforms PKC epsilon, PKC gamma, PKC theta and PKC zeta and specific conditions and diseases, one of ordinary skill in this

art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

The above consideration justifies that conclusion here; undue experimentation would be required to practice Applicants' invention as presently claimed.

Claims 32, 33 and 37-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Formula I compounds and their salts, pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, tautomers and stereochemical isomers, does not reasonably provide enablement for isomers thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace all isomers broadly, are not enabled. Isomers are compounds with the same molecular formula but different structural formulae. Contingent upon the type of isomer, isomers do not always share the same physical and chemical properties. Applicant bears the burden to show in full, clear and exact terms that the instantly claimed subject matter, which is Isomers, do indeed or

necessarily share analogous properties. There are many different classes of isomers, such as stereoisomers, enantiomers, geometrical isomers, etc. One skilled in the art could not predict that the different types of isomers of the instant compound claimed with have the physiochemical properties. The art teaches that the skilled artisan can not extrapolate physiochemical properties from one isomeric form to another. No evidence of record in the form of adequate representations broadly depict methods for making or using isomers of the instant compounds. Applicants should limit the claims accordingly.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 33, 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims

Rejections Under 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 32, 33 and 37-49, are rejected under 35 USC 103(a) over Muro, et al., US 4997834, issued Mar. 5, 1991 describing 4-amino(alkyl)-1-pyridylcarbamoylcyclohexane compounds that possess hypertensive and cerebral coronary vasodilating action and renal and peripheral circulation improving action, *inter alia*. Note at least compound (11), Trans-4-(1-piperidinyl)methyl-1-(4-pyridylcarbamoyl)cyclohexane, which is a position isomer and alkyl homolog of compounds of the present claims, when Ring(1) is pyridine, when Ring(3) is 1,4-cyclohexylene, optionally substituted with C1-C6 alkyl, when n is 1, NRbRc is piperidine, and when X, Ra, R1 and Rb are each independently

hydrogen or C1-C6 alkyl. Compare at least this Muro compound to at least the second compound of claim 37.

One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds that are position isomers and/or alkyl homologs of the Muro compounds, because such structurally related compounds are expected to possess similar properties. It has been held that compounds that are structurally isomeric and/or homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results.

> An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.

In re Payne, 203 USPQ 245, 254 (CCPA 1979). See also *In re Papesch*, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 16 USPQ2d 1897 (Fed.Cir. 1991) (discussed in MPEP § 2144) for an extensive case law review pertaining to obviousness based on close structural chemical compound similarity. See also MPEP § 2144.08, I[II.A.4(c). Compounds that are isomers (compounds that have the same functional groups arranged is a different positional format) and/or homologs (compounds differing by the successive addition of the same chemical group, e.g., by alkylene groups), as here, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 195 USPQ 426 (CCPA 1977). Muro establishes a prima facie case of obviousness for the presently claimed

compounds. Absent the presentation of verifiable data establishing the unobviousness of the claimed compounds over Muro, this rejection is sound.

Claims 32, 33 and 37-49, are rejected under 35 USC 103(a) over Arita I, et al., US 5478838, issued Dec. 26, 1995 describing 4-amino(alkyl)cyclohexane-1-carboxamide compounds having hypertensive action, *inter alia*. Note compounds of Formulas (I), (Ia) and (Ib) at col. 2, line 1 - to col. 5, line 26 and the specific compounds at col. 6, line 5+, of Examples 8, 13, 21, and 35-37, *inter alia*. Where Arita I describes the specific compounds 8, 13, 21, and 35-37, *inter alia*; teaches generically that the compounds of Formulas (I), (Ia) and (Ib) may have the ring containing X, N, R5, R6 and R8 (the cognate of Ring (1) in the present claims) be a pyridine; and R1 and R2 ((together with the nitrogen to which they are connected; the cognate of –N-(Rb)(Rc) in the claimed compounds)) can be alkylidene or phenylalkylidene; the chemist of ordinary skill would be well motivated to prepare the compounds of the present claims. The genus of Arita I (col. 2, line 10- to col. 6,line 27) is small enough to suggest the presently claimed compounds, especially when viewed in light of the specific compounds prepared in Arita I. The skilled chemist would be well motivated to prepare the presently claimed compounds with the expectation that they would have the utility described by Arita I.

Claims 32, 33 and 37-49, are rejected under 35 USC 103(a) over Arita II, et al., US 5958944, issued Sep. 28, 1999 describing pyridyl-aminoalkyl-benzamide

compounds having hypertensive action, *inter alia*. Note the compounds of Formula (I) at col. 2, line 10 - to col. 6, line 27 and the specific compounds 1-193, 196, 220-224, 540 and compounds 545, 546 and 548, *inter alia*. Where Arita II describes the specific compounds 1-193, 196, 220-224 and 540;\, teaches generically that the compounds of Formula (I) may have R and R1, together with the nitrogen to which they are connected (the cognate of -N-(Rb)(Rc) in the claimed compounds), be a heterocycle; exemplifies that heterocycle as pyrrolidino, piperidino, piperazino, and imidazolo (col. 4, lines 8-18, inter alia); and prepares compounds 545, 546 and 548 with those specific heterocycles; the chemist of ordinary skill would be well motivated to prepare the compounds of the present claims with the expectation that they would have the utility described by Arita II. The genus of Arita II (col. 2, line 10- to col. 6,line 27) is small enough to suggest the presently claimed compounds, especially when viewed in light of the specific compounds prepared in Arita II.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CECILIA M. JAISLE, J.D. whose telephone number is (571)272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

CECILIA M. JAISLE, J.D.
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